Novel Homozygous Variant in *SLC25A1* Gene in a Saudi Patient

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Background and Objectives

Biallelic pathogenic missense and truncating variants in *SLC25A1* gene have been associated with inborn error of metabolism combined D-2- and L-2-hydroxyglutaric aciduria (D,L-2-HGA). *SLC25A1* deficiency is autosomal recessive disease manifested clinically as neonatal encephalopathy, respiratory insufficiency, developmental delay, hypotonia, and early death. This neurometabolic disorder is characterized biochemically by elevated levels of both D-2-HG and L-2-HG in body fluids. We aim to contribute to the medical efforts of diagnosing mitochondrial and metabolic disorders by reporting a novel variant among the Saudi population with its clinical manifestation.

Case Report and Methods

We are reporting a 3 year and 6 month old Saudi boy, the 2nd son to a consanguineous parents with a healthy older son. At the age of 3 days, he was noted to have twitching movement with decerebrate position of the upper limb and desaturation (pre- and post ductal) down to 40%. He was admitted urgently to the NICU, where he was diagnosed with grade 3 intraventricular hemorrhage, neonatal hypoglycemia, ventricular septal defect and congenital cataract with a suspicion of metabolic disorder.

At the age of 5 months, he was referred to our hospital for metabolic work up and further management. He presented with delayed fine motor development, delayed gross motor development, abnormal facial shape, generalized hypotonia and seizures (on anticonvulsant). A brain MRI showed supratentorial hydrocephalus with tortuous optic nerves. His urine organic acid profile reported elevated 2-hydroxyglutarate. Whole exome sequencing (WES) then segregation analysis by Sanger sequencing were requested.

Results

WES detected a homozygous splice deletion NM_005984.5: c.95-3delC (NM_001256534.1: c.113del p.Ala38Glufs*19) in *SLC25A1* gene. Segregation analysis through Sanger sequencing confirmed this deletion in the index patient and detected it in the healthy mother and father in heterozygous state, thus confirming their carrier status. The variant was not detected in the healthy brother.

Conclusion

Differential diagnosis of *SLC25A1* deficiency should be considered in newborns with similar phenotype especially when 2-hydroxyglutarate is elevated in body fluids. Although the pathogenicity of the novel splice deletion c.95-3delC has not been functionally proven yet, it could be classified as likely pathogenic. We recommend adding this novel deletion to the databases of known Saudi and Arab variants, as this would help in future carriership testing and premarital screening programs.